Perioperative Analgesia in Rodents

The Public Health Service Policy on Humane Care and Use of Laboratory Animals states that procedures on animals that may cause more than momentary or slight pain or distress should be performed with appropriate sedation, analgesia or anesthesia. Procedures that cause pain or distress in human beings are now considered to cause pain or distress in animals. While NCI-Frederick fully recognizes the difficulties in objectively assessing perioperative pain in rodents, the NCI-Frederick Animal Care and Use Committee (ACUC) has taken the position that rodents undergoing major surgical procedures must routinely receive the benefit of perioperative analgesic administration unless justified. In general, **major surgery** includes any surgery that penetrates and exposes a body cavity or produces substantial impairment of physical or physiologic functions (such as laparotomy, thoracotomy and craniotomy). **Minor surgery** includes procedures such as skin biopsy, tail clipping, castration, subcutaneous tumor removal, etc. In this case, animals will be monitored for signs of pain or distress, and if found; post-operative analgesia will be administered. Signs of pain and distress include: decreased movement, aggression when handled, failure to groom, ruffled coat, and abnormal posture.

In adopting this position, the NCI-Frederick ACUC recognizes that there may be occasions when analgesic use would interfere with the scientific objectives of a study. In such cases, the Principal Investigator can request an exception to the ACUC position by including a written scientific justification (e.g. study involves the liver and analgesic is metabolized by the liver) in the animal study proposal for review and approval by the NCI-Frederick ACUC.

The analgesic agents listed below have been used successfully in rodents. The selected analgesic should be administered before the animal recovers from anesthesia, depending on the compound. While a single dose of a relatively long-acting analgesic is expected to alleviate the pain and distress associated with the immediate post-operative period, this initial dosing should be followed by an evaluation of the animal at the expected end of the analgesic's duration, to see if subsequent dosing is required. If you have any questions regarding appropriate analgesia, contact the Laboratory Animal Medicine office at 846-5195.

The first four drugs are recommended for their ease of administration. All drugs given PO (Per Os) can be administered in water bottles or in nutritional Jell-O supplements.

1. Bupivacaine (Marcaine)	**mouse and rat:** 2 mg/kg, intrathoracic or intra-abdominal, before closure, 6-8 hour duration; approximately 1-3 drops [1 drop for each centimeter of the incision size] of the 0.25% concentration
2. Acetaminophen	**mouse:** 300mg/kg, PO, 6-8 hour duration **rat:** 100-300mg/kg, PO, 4-6 hour duration
3. Ibuprofen	**mouse:** 7.5mg/kg, PO, 4-6 hour duration **rat:** 10-30mg/kg, PO, 4-6 hour duration
4. Aspirin	**mouse and rat:** 100-300mg/kg, PO, 4-6 hour duration
5. Flunixin	**mouse and rat:** 2.5 mg/kg, SC BID, 3-4 hour duration
6. Ketoprofen/ Carprofen	**mouse and rat:** Ketoprofen 1 mg/kg SC; Carprofen 5 mg/kg SC
7. Butorphanol* (Torbugesic)	**mouse:** 1-5 mg/kg, SC BID, 3-4 hour duration **rat:** 2 mg/kg, SC BID, 3-4 hour duration

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8. Buprenorphine* (Buprenex) **mouse:** 0.05-0.1mg/kg, SC, 8-12 hour duration
rat: 0.01-0.25 mg/kg, SC, 8-12 hour duration

**Controlled substances; purchase with approval from the Controlled Substance Coordinator.*

Drug Information

Bupivacaine

Related chemically and pharmacologically to the aminoacyl local anesthetics. It is a homologue of mepivacaine and is chemically related to lidocaine. Local anesthetics block the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential. Systemic absorption of local anesthetics produces affects on the cardiovascular and central nervous systems. At normal therapeutic doses, changes on the heart are minimal. The onset of action with bupivacaine is rapid and there is a long period of analgesia following administration. Depending on the route of administration, local anesthetics are distributed to some extent to all body tissues, with high concentrations found in highly perfused organs such as the liver, lungs, heart and brain. Metabolism occurs in the liver and the kidney is the main excretory organ. When administered in recommended doses and concentrations, bupivacaine does not ordinarily produce irritation or tissue damage.

Acetaminophen

A non-steroidal anti-inflammatory that has similar analgesic efficacy to aspirin but has little anti-inflammatory activity. It is rapidly absorbed from the upper gastrointestinal tract with peak plasma levels occurring between 30 and 60 minutes after therapeutic doses. The parent compound, which is nontoxic is extensively metabolized in the liver to form principally the sulfate and glucuronide conjugates which are also nontoxic and are rapidly excreted in the urine. A small fraction of an ingested dose is metabolized in the liver by the cytochrome P-450 mixed function oxidase enzyme system to form a reactive, potentially toxic, intermediate metabolite which preferentially conjugates with hepatic glutathione to form nontoxic cysteine and mercapturic acid derivatives which are then excreted by the kidney. Ingestion of a large overdose saturates the glucuronide and sulfate conjugation pathways, resulting in a larger fraction of the drug being metabolized via the P-450 pathway. This increase may deplete hepatic stores of glutathione, resulting in cellular necrosis. Acetaminophen does not affect platelet count.

Ibuprofen

A nonsteroidal anti-inflammatory drug that possesses anti-inflammatory, analgesic and antipyretic activity. Its mode of action is not completely understood, but may be related to prostaglandin synthesis inhibition. Ibuprofen is well absorbed orally, with peak plasma levels usually occurring within 1-2 hours. Following oral administration, the majority of the dose was recovered in the urine within 24 hours. The remainder of the drug was found in the stool as both metabolites and unabsorbed drug. It is rapidly metabolized and eliminated in the urine. The excretion of ibuprofen is virtually complete 24 hours after the last dose. We suspect that it might reduce the platelet count as it does in humans.

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Aspirin

Sometimes known as acetylsalicylic acid inhibits cyclooxygenase (prostaglandin synthetase) thereby reducing the synthesis of prostaglandins and thromboxanes. It causes an irreversible effect on platelet aggregation. Aspirin is rapidly absorbed from the stomach and proximal small intestine in monogastric animals. Highest levels may be found in the liver, heart, lungs, renal cortex and plasma. Salicylate is metabolized in the liver primarily by conjugation with glycine and glucuronic acid via glucuronyl transferase. The kidneys rapidly excrete salicylate and its metabolites by both filtration and renal tubular secretion.

Butorphanol

A synthetic opiate partial agonist, butorphanol is related structurally to morphine but exhibits pharmacological actions similar to other partial agonists. Its agonist activity is thought to be exerted at the kappa and sigma receptors and the analgesic actions at sites in the limbic system (sub-cortical level and spinal levels). Butorphanol is well distributed, with highest levels found in the liver, kidneys and intestine. Concentrations in the lungs, endocrine tissues, spleen, heart, fat tissue and blood cells are also higher than those found in the plasma. It is metabolized in the liver, primarily by hydroxylation. Metabolites and the parent compound are mainly excreted into the urine (only 5% is excreted unchanged), but 11-14% of a dose is excreted into the bile and eliminated with the feces.

Buprenorphine

A thebaine derivative, buprenorphine is a synthetic partial opiate agonist. It has partial agonist activity at the mu receptor and is considered to be 30 times as potent as morphine and exhibits many of the same actions as the opiate agonists. The cardiovascular effects of buprenorphine may cause a decrease in both blood pressure and cardiac rate. It concentrates in the liver, but is also found in the brain, GI tract and placenta. It is metabolized in the liver by N-dealkylation and glucuronidation. These metabolites are then eliminated by biliary excretion into the feces (70%) and urinary excretion (27%). It has been reported that use of buprenorphine can cause a decrease in IL2 and IL18 production.

Flunixin

A nonsteriodal anti-inflammatory agent that is a highly substituted derivative of nicitonic acid. It is a very potent inhibitor of cyclooxygenase and like other NSAIDS, it exhibits analgesic, anti-inflammatory and antipyrexic activity. It should be used with caution in animals with pre-existing GI ulcers, renal, hepatic or hematologic diseases.

Ketoprofen

A proprionic acid derivative nonsteroidal anti-inflammatory agent. Like other NSAIDS, ketoprofen exhibits analgesic, anti-inflammatory and antipyrexic activity. Its purported mechanism of action is the inhibition of cyclooxygenase catalysis of arachidonic acid to prostaglandin precursors (endoperoxides), thereby inhibiting the synthesis of prostaglandins in tissues. Ketoprofen purportedly has inhibitory activity on lipoxygenase.

Carprofen

A proprionic acid derivative nonsteroidal anti-inflammatory agent. Like other NSAIDS, carprofen exhibits analgesic, anti-inflammatory and antipyrexic activity probably through its inhibition of cyclooxygenase, phospholipase A_2 and inhibition of prostaglandin synthesis.

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